PERSPECTIVES

NMDA receptor antagonists: tools in neuroscience with promise for treating CNS pathologies

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NMDA receptors (NMDARs) are essential for normal physiological processes in the central nervous system, e.g. development, induction of synaptic plasticity, learning and memory. Excessive activation of NMDARs can lead to neuronal damage in many acute (hypoxic–ischaemic injury) and chronic neurodegenerative diseases (Alzheimer, Parkinson, Huntington). This dual role of NMDARs in normal and abnormal brain functioning imposes constraints on possible therapeutic strategies involving NMDAR antagonists. Blockade of excessive NMDAR activity must therefore be achieved without interference with physiological activity.

As of today, three major classes of NMDAR antagonists can be distinguished based on their mechanism of action. Competitive NMDAR antagonists act at the agonist (glutamate) or co-agonist (glycine) site, non-competitive NMDAR allosteric inhibitors act at extracellular domains (e.g. Zn^{2+}, H^+, NO), and NMDAR channel blockers block the open channel following activation by the agonists. All competitive antagonists discriminate poorly between the different NMDAR subtypes NR1/NR2(A–D) (Paoletti & Neyton, 2007) and therefore cause generalized inhibition of NMDARs. Due to the often adverse CNS effects, including drowsiness, hallucinations and even coma, most of the competitive NMDAR antagonists failed in clinical trials. However, ifenprodil and its derivatives (CP-101,606 and Ro25-6981), which are non-competitive high-affinity NR2B-selective antagonists, are better tolerated than the broad-spectrum competitive antagonists. Interestingly, ifenprodil is more efficient at high levels of glutamate (activity/use dependence) and at low pH (pH dependence) (Paoletti & Neyton, 2007). These two features are attractive for clinical use, since pathological conditions are often accompanied by high glutamate levels and/or strong acidification, e.g. within an ischaemic core. Still, none of the NR2B-selective antagonists completed clinical trials, although they were effective in animal models of ischaemic brain injury (Paoletti & Neyton, 2007). In contrast, the channel blocker memantine was recently approved for the treatment of moderate-to-severe Alzheimer's disease. Memantine's unusual clinical tolerance may well reflect its low affinity binding to open channels and its relatively fast unblocking kinetics (Johnson & Kotermanski, 2006; Lipton, 2006).

In the current issue of *The Journal of Physiology*, Dravid and colleagues (Dravid *et al.* 2007) investigated the proton sensitivity (pH 7.6 *versus* pH 6.9) of a wide range of NMDAR channel blockers at four NR1/NR2 combinations. They found that several channel blockers, including the two MK-801 stereoisomers, sense the protonation status of both recombinant and neuronal NMDAR proteins. Blockers remaining trapped in the pore during agonist unbinding, like ketamine or (−)MK-801, showed stronger dependence on extracellular pH than others, like (+)MK-801, memantine or dextromethorphan (for a complete list, see Table 2 of Dravid *et al.* 2007). Acidic extracellular pH increased the association rate of (−)MK-801 with the intrapore binding site of the NMDAR, which appears to be the underlying mechanism for pH-dependent potency boost. This potency boost was > 5-fold for NR1/NR2A receptors but nearly absent for NR1/NR2(B–D) receptors, suggesting that either kinetics or structural determinants of channel block are influenced by NR2 subunits. Yet, the pH-dependent potency boost of NMDAR channel blockers is intriguing and requires further investigations, since low pH reduces the open probability of NMDARs (for review, see Erreger *et al.* 2004), and should thus decrease the apparent association rate by reducing the opportunity for channel blocker binding.

The physical location of the proton sensor within the NMDAR channel complex is still unknown, but former mutagenesis studies of NMDAR subunits suggest a tight coupling between proton sensor and gating determinants (for review, see Erreger *et al.* 2004). The present study provides data suggesting that the effects of protons on (−)MK-801 but not (+)MK-801 potency reflect actions at the extracellular proton site of the NMDAR. In case of the NR2A subunit, the proton affinity at its amino-terminal modulatory domain increases after Zn^{2+} binding, leading to enhanced protonation of the NMDAR at physiological pH (Erreger *et al.* 2004). Dravid *et al.* (2007) made use of this effect to demonstrate that the potency of (−)MK-801 increased in the presence of 1 μM Zn^{2+}, comparable to a potency increase produced by a drop in pH from 7.6 to 6.9. These results raise the possibility that the differential potency of the MK-801 stereoisomers reflects the ability of (−)MK-801 to sense the protonation of the NMDAR or to sense biophysical alterations of NMDAR protonation. Notably, the ionization state of an NMDAR channel blocker usually does not affect its efficacy, except for ketamine, whose potency increases with protonation (MacDonald *et al.* 1991).

Another salient observation by Dravid *et al.* (2007) is that the potency of channel block of a structurally diverse group of compounds varies for NMDARs with different NR2 subunits, even at physiological pH. The > 10-fold higher potency of (−)MK-801 and (+)ketamine for NR1/NR2B *versus* NR1/NR2A receptors could be the basis for the development of new truly subunit-selective NMDAR channel blockers. Clinically promising subunit-selective NMDAR channel blockers should show in addition pH dependence and, similar to memantine, fast channel unblocking kinetics to prevent the drug from occupying the channels and interfering with normal synaptic transmission. Memantine is therefore very different from (+)MK-801, which binds with higher affinity and has relatively slower unblocking kinetics. Because of these properties (+)MK-801 has been used for the last 20 years as a pharmacological tool to irreversibly block NMDARs but has failed in clinical trials.

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